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PATENT SPECIFICATION

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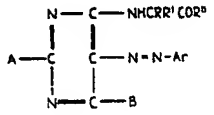
COMPLETE SPECIFICATION

New Pyrimidine Derivatives and their Use in the Manufacture of Pteridin Derivatives

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates in the first place to new pyrimidine derivatives and to a process for making them.

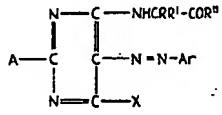
The new pyrimidine derivatives of this invention are compounds of the general formula:—



wherein A stands for hydroxyl, amino or alkylamino groups, wherein B stands for hydroxyl, thiol, alkylthio, amino or mono- or di-substituted amino groups, wherein Ar is an aryl radical which optionally may bear substituents, wherein R and R^1 may be hydrogen, hydrocarbon, or substituted hydrocarbon radicals and one of them, but not both at once, may be the group $—COR^{11}$, and wherein R^{11} is hydrogen, a hydrocarbon radical which may contain substituents or a hydrocarbon-oxy radical, or an amino or mono-substituted-amino group.

The said new pyrimidine derivatives are useful as intermediates in the manufacture of substances of chemotherapeutic value, for example of folic acid and related compounds.

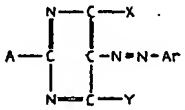
They may be manufactured, and it is a further feature of the invention so to manufacture them, by a process which comprises reacting a pyrimidine derivative of the formula:—



wherein A, Ar, R, R^1 and R^{11} have the meaning stated above and X stands for a halogen atom, with reagents capable of the replacement of an active halogen substituent by hydroxyl, thiol, alkylthio, amino or mono- or di-substituted amino groups.

Such reagents are for example alkali metal hydroxides; hydrogen sulphide or alkali metal hydrosulphides, alkali metal mercaptides; ammonia or primary or secondary amines. In the case where R^{11} stands for hydrocarbonoxy and the reactant is a primary amine the hydrocarbonoxy group as well as the group X may be replaced by a mono-substituted amino group.

In the case of those new compounds of the invention represented by the above formula wherein B is a hydroxyl, thiol, amino or alkylamino group they may also be made by a process which comprises reacting a pyrimidine derivative of the formula:—



wherein A and Ar have the meaning

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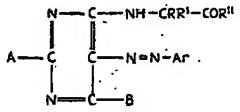
stated above, wherein Y is a hydroxyl, thiol, amino or mono-substituted amino group, and wherein X stands for a halogen atom, with an α-amino-aldehyde, -ketone or -carboxylic acid ester or amide of the formula:—

$$NH_2—CRR^1—COR^{11}$$

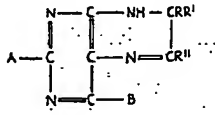
wherein R, R^1 and R^{11} have the significance stated above.

Where R^{11} is hydrogen or hydrocarbon, i.e. where the starting material is an amino-aldehyde or -ketone, this may be used in the form of a functional derivative thereof, for example of an acetal, oxime or semi-carbazone thereof, the product being then subsequently liberated from e.g. its acetal, oxime or semicarbazone by hydrolysis.

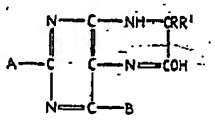
By yet a further feature of the invention we provide a process for the manufacture of derivatives of pteridin which comprises reacting upon the aforesaid pyrimidine derivatives of the formula



by means of reducing agents so that the —N=N—Ar group is converted to an $—NH_2$ group, the so-formed amino-compound being then either permitted spontaneously, or constrained, for example, by heat, to undergo ring closure with formation of, where R^{11} is hydrogen or hydrocarbon, pteridin derivatives of the formula:—



or, where R^{11} is a hydrocarbon-oxy, amino- or mono-substituted amino group, pteridin derivatives of the formula:—



with elimination, as will be understood, in the first case of water and in the second case of the alcohol $R^{11}H$, ammonia or a primary amine.

The said pteridin derivatives, which are di-hydropteridins, may, when at least one of R and R^1 is hydrogen, as is known, be converted to the corresponding pteridin by oxidation.

The invention is illustrated but not limited by the following Examples in which the parts are by weight.

EXAMPLE 1.

12 Parts of 2 - amino - 4 - methoxy-6-chloropyrimidine are dissolved in 50 parts of cold concentrated hydrochloric acid and the solution is heated on the steam-bath during 30 minutes. The mixture is then cooled, diluted with 200 parts of water and filtered. The solid residue consists of 2 - amino-4-hydroxy-6-chloro-pyrimidine, m.p. 261° C.

87 Parts of 2 - amino - 4 - hydroxy-6-chloropyrimidine, made as described above, are dissolved in 3600 parts of 0.2N sodium hydroxide and 120 parts of sodium carbonate are added to the solution. A solution of benzenediazonium chloride prepared from 56 parts of aniline is added to the stirred solution during one hour. The mixture is stirred for a further 12 hours and is then filtered and the solid residue is washed successively with water, alcohol and ether. It consists of 2-amino-4-hydroxy - 5 - benzeneazo-6-chloropyrimidine.

38 Parts of aminoacetone hydrochloride are dissolved in 250 parts of ethyl alcohol and to the solution there is added a solution of 48 parts of semicarbazide hydrochloride in 100 parts of water. The mixture is permitted to stand for 2 hours and is then filtered and the solid residue is recrystallised from aqueous alcohol and consists of aminoacetone - semicarbazone hydrochloride, m.p. 212° C.

107 Parts of aminoacetonesemicarbazone hydrochloride, made as described above, is added to a cold solution of 43.7 parts of sodium ethoxide in 600 parts of ethyl alcohol and the mixture is stirred for 2 hours. It is then added to a cold solution of 75 parts of 2-amino-4-hydroxy-5 - benzeneazo-6-chloropyrimidine, made as described above, in 400 parts of dimethylformamide. It is allowed to stand for 12 hours and then filtered and the residual solid is washed successively with alcohol and water. There is obtained 2-amino-4-hydroxy - 5 - benzeneazo - 6 - acetonylaminopyrimidine semicarbazone, m.p. 206° C.

81 Parts of 2 - amino - 4 - hydroxy-5-benzeneazo-6 - acetonylaminopyrimidine-semicarbazone is dissolved in 250 parts of glacial acetic acid and to the solution there are added 1500 parts of 2N hydrochloric acid. The mixture is allowed to stand for 30 minutes and is then filtered and the residual solid is crystallised from ethyl alcohol. There is obtained 2-amino-4 - hydroxy-5-benzeneazo - 6 - acetonyl-

aminopyrimidine hydrochloride of m.p. higher than 300° C. The free base liberated from this salt has m.p. 183° C.

51 Parts of 2 - amino - 4 - hydroxy-5-benzeneazo - 6 - acetonylaminopyrimidine hydrochloride are dissolved in 250 parts of glacial acetic acid and the solution is stirred and heated to 80—90° C. and 40 parts of zinc dust are added to it during 30 minutes. The mixture is then filtered and 500 parts of 5N hydrochloric acid are added to the filtrate which is then again filtered and the solid residue consists of 2 - amino-6-hydroxy-8-methyl-9 : 10 - dihydropteridin hydrochloride monohydrate, m.p. not below 300° C.

16.3 Parts of 2 - amino - 6 - hydroxy-8-methyl - 9:10 - dihydropteridin hydrochloride monohydrate are dissolved in 1200 parts of 0.25N aqueous sodium hydroxide solution. To the stirred solution there are added 243 parts of 0.2N aqueous potassium permanganate solution during one hour. The mixture is then filtered and carbon dioxide is passed into the filtrate which is then again filtered. The solid residue consists of 2-amino - 6 - hydroxy - 8 - methylpteridin, m.p. not below 300° C.

EXAMPLE 2.

1.2 Parts of glycine ethyl ester hydrochloride are added to a solution of 0.53 part of sodium ethoxide in 5 parts of ethyl alcohol the mixture being stirred for 30 minutes. It is then added to a solution of 1 part of 2-amino-4-hydroxy-5-benzeneazo - 6 - chloropyrimidine, made as described in Example 1, in 5 parts of dimethylformamide and the mixture is allowed to stand for 12 hours and is then filtered. The solid residue is washed successively with ethyl alcohol and water and consists of 2-amino - 4 - hydroxy-5-benzeneazo - 6 - carboethoxymethylamino-pyrimidine which, when crystallised from *n*-butanol, has m.p. 238° C.

1 Part of 2 - amino - 4 - hydroxy-5-benzeneazo-6 - carboethoxymethylamino-pyrimidine, made as described above, is dissolved in 5 parts of glacial acetic acid and the solution is stirred and heated to 80—90° C. and then an excess of zinc dust is added slowly. The fine suspension of white solid is decanted from unused zinc dust and is then centrifuged. The so-separated solid is dissolved in boiling 0.25 N sulphuric acid and from the solution, when cold, there are filtered off colourless crystals of 9:10-dihydroxanthopterin sulphate, m.p. not below 300° C.

EXAMPLE 3.

In the process of Example 2 the glycine ethyl ester hydrochloride and the sodium ethoxide are replaced by equivalent quantities of glycine isopropyl ester hydrochloride and sodium isopropoxide respectively, and there is thus obtained isopropyl 2-amino-4-hydroxy-5-benzeneazo-6-pyrimidylamino acetate of m.p. 222° C.

EXAMPLE 4.

The glycine ethyl ester hydrochloride in the process of Example 2 is replaced by an equivalent quantity of alanine ethyl ester hydrochloride and there is obtained ethyl α-(2-amino-4-hydroxy-5-benzeneazo-6- pyrimidylamino)propionate of m.p. 214° C.

EXAMPLE 5.

To 144 parts of 2:4-diamino-6-chloropyrimidine dissolved in 1000 parts of cold water there is added a solution of *p*-chlorobenzene - diazonium chloride prepared from 130 parts of *p*-chloroaniline. Sufficient sodium acetate is added to the mixture to bring the pH to 5.0 and it is stirred for 24 hours. The yellow precipitate of 2:4-diamino-6-chloro-5-*p*-chlorobenzeneazopyrimidine of m.p. 270° C. is filtered off and dried.

97 Parts of glycine ethyl ester hydrochloride are added to a solution of 47 parts of sodium ethoxide in 260 parts of ethyl alcohol and the mixture is stirred for 15 minutes. It is then added to a solution of 49 parts of 2:4-diamino-6-chloro-5-*p*-chlorobenzeneazopyrimidine in 800 parts of dimethylformamide and the mixture is stirred at 60—70° C. for 12 hours. It is then filtered and the filtrate is concentrated to 200 parts by distillation under reduced pressure. There is then added an equal quantity of water and 2:4-diamino-5-*p*-chloro - benzeneazo - 6-carboethoxymethylaminopyrimidine of m.p 202° C. is filtered off and dried.

8 Parts of 2:4 - diamino-5-*p*-chlorobenzeneazo-6 - carboethoxymethylamino-pyrimidine made as described above, are dissolved in 20 parts of glacial acetic acid and the solution is heated to 80° C. 13 Parts of zinc dust are then added with stirring and the mixture is boiled until the zinc is dissolved. It is then filtered hot and the filtrate is cooled and 2:6-diamino-8-hydroxy-9:10 - dihydropterin acetate is filtered off, dissolved in 200 parts of warm water. The solution is mixed with 50 parts of 2N sulphuric acid and filtered. 2:6 - Diamino-8-hydroxy-9:10 - dihydropteridin sulphate is obtained, of m.p. above 300° C.

EXAMPLE 6.

225 Parts of glycidylphenyl ether and 199 parts phthalimide are heated together at 160° C. for 2 hours. The mixture is then cooled and crystallised from ethyl alcohol to give 318 parts of 1-phthalimido-3-phenoxy-2-propanol of m.p. 117° C.

116 Parts of 1-phthalimido-3-phenoxy-2-propanol are dissolved in 400 parts of glacial acetic acid and the solution is heated at 50° C. A solution of 47 parts of chromic anhydride in 80 parts of glacial acetic acid is then added with stirring, the temperature being maintained below 50° C. The mixture is then cooled and filtered and there is obtained 1 - phthalimido - 3 - phenoxy-propanone-2 of m.p. 165° C.

4.4 Parts of 1-phthalimido-3-phenoxy-propanone-2 is dissolved in 100 parts of glacial acetic acid and the solution is mixed at 60° C. with a solution of 1.7 parts of semicarbazide hydrochloride and 2.5 parts of crystalline sodium acetate in 10 parts of water. The semicarbazone of 1-phthalimido-3-phenoxypropanone - 2 is filtered off and crystallised from *n*-butanol; it has m.p. 193° C.

9.8 Parts of the semicarbazone of 1-phthalimido-3 - phenoxypropanone - 2 is suspended in 45 parts of ethyl alcohol and a solution of 1.3 parts of sodium hydroxide in 20 parts of water. At the end of 1 hour the almost clear solution is filtered and the alcohol is distilled from the filtrate under reduced pressure. 4.7 Parts of concentrated hydrochloric acid are then added below 50° C.; the mixture is filtered and the solid is suspended in 25 parts of ethyl alcohol and heated to 90° C. for 30 minutes with 12 parts of 0.33 N hydrochloric acid. The resulting solution is evaporated to a syrup under reduced pressure. It is then treated with 50 parts of water, filtered and the filtrate is evaporated to dryness. The residue is crystallised from ethyl alcohol to give the hydrochloride of the semicarbazone of 1 - amino - 3-phenoxy-propanone-2, of m.p. 201° C.

22.5 Parts of the hydrochloride of the semicarbazone of 1-amino - 3 - phenoxy-propanone-2 are added to a cold solution of 5.9 parts of sodium ethoxide in 90 parts of ethyl alcohol, to which have been added 7.5 parts of sodium bicarbonate and a solution of 14.5 parts of 2-amino-4-hydroxy - 5 - benzeneazo - 6 - chloro-pyrimidine in 100 parts of dimethyl-formamide. The mixture is stirred for 24 hours, filtered and the solid washed with ethyl acetate and water; it consists of the semicarbazone of 1-phenoxy-3-(2¹-amino-4¹-hydroxy-5¹-benzeneazo-6¹ - pyrimidyl-amino)acetone which melts at 265° C. with decomposition. 16.5 Parts of this semicarbazone are dissolved in 65 parts of glacial acetic acid and to this solution are added 78 parts of 5N hydrochloric acid. The mixture is allowed to stand and after one hour is filtered. 1-Phenoxy-3-(2¹-amino-4¹-hydroxy - 5¹ - benzeneazo - 6¹-pyrimidylamino)acetone hydrochloride of m.p. 192° C. with decomposition is filtered off and dried.

EXAMPLE 7.

30 Parts of 4-chloro-2:6-dimethoxy-pyrimidine and 180 parts of 20% hydrochloric acid are heated together at to 80° C. for 30 minutes; 200 parts of water are then added and the solid which separates is filtered off. This is washed with light petroleum and the residual 4-chloro-2:6-dihydroxypyrimidine is crystallised from water. It has m.p. 300° C.

29.5 Parts of 4-chloro-2:6-dihydroxy-pyrimidine are dissolved in 2000 parts of hot water and the solution is cooled rapidly to 0° C., 34 parts of sodium bicarbonate are then added followed by a solution of *p*-toluenediazonium chloride prepared from 21.5 parts of *p*-toluidine. The mixture is stirred for 84 hours and then filtered. The solid is ground with an excess of dilute hydrochloric acid, filtered, washed with water and dried. It consists of 4 - chloro-2:6-dihydroxy-5-*p*-tolueneazopyrimidine of m.p. 240° C. with decomposition.

To a cold solution of sodium methoxide prepared by dissolving 3.7 parts of sodium in 75 parts of methyl alcohol there are added 20 parts of glycine methyl ester hydrochloride followed by 19.4 parts of 4-chloro-2:6-dihydroxy-5 - *p* - tolueneazo-pyrimidine in 1000 parts of dimethyl formamide. The mixture is stirred for 17 hours and filtered. The solid residue is washed, first with water and then with methyl alcohol to give methyl 2:6-dihydroxy-5-*p*-tolueneazo - 4 - pyrimidyl-aminoacetate of m.p. 272° C. with de-composition.

1.6 Parts of methyl 2:6-dihydroxy-5-*p*-tolueneazo-4-pyrimidylaminoacetate is suspended in 25 parts of water, containing 5 parts of 2N sodium hydroxide. 3 Parts of sodium hydrosulphite is then added slowly at 50° C. The mixture is then boiled, acidified and filtered. The residue consists of 2:6:8-trihydroxy-9:10-dihydropteridin which does not melt below 300° C.

EXAMPLE 8.

29 Parts of 4-chlorocytosine are finely ground and suspended in 3000 parts of water and the suspension is mixed with 34 parts of sodium bicarbonate and a solution of *p* - toluenediazonium chloride prepared from 21.5 parts of *p*-toluidine is added. The mixture is stirred for 17 hours and filtered. The solid residue consists of 6-amino-4-chloro-2-hydroxy-5-*p*-tolueneazopyrimidine.

This substance is then condensed with glycine methyl ester by the process described in Example 7, to give methyl

4-amino-2-hydroxy - 5 - *p* - toluencazo-6-pyrimidylaminoacetate of m.p. 300° C., with decomposition.

EXAMPLE 9.

42 Parts of glycine ethyl ester hydrochloride are dissolved in a cold solution of sodium ethoxide prepared from 6.9 parts of sodium and 450 parts of ethyl alcohol and to this solution there are added 24 parts of 2-amino-4:6-dichloropyrimidine. The mixture is boiled under reflux for 12 hours. It is then cooled and filtered and the filtrate is evaporated to dryness. The residue is triturated with water and filtered. There is obtained ethyl 2 - amino - 4 - chloro - 6-pyrimidylaminoacetate which is crystallised from toluene and has m.p. 151° C. 46 Parts of ethyl 2-amino-4-chloro-6-pyrimidylaminoacetate are dissolved in 1000 parts of glacial acetic acid and mixed with a solution of *p*-chlorobenzenediazonium chloride prepared from 25.5 parts of *p*-chloroaniline together with 60 parts of crystallised sodium acetate. The mixture is stirred for 3 days and ethyl 2-amino-4-chloro-5 - *p*-chlorobenzeneazo - 6-pyrimidylaminoacetate of m.p. 210° C. is filtered off.

2 Parts of this substance are suspended in 90 parts of ethyl alcohol and 30 parts of 2N sodium hydrosulphide are added and the mixture is boiled under reflux for 3 hours and then filtered hot. The filtrate is cooled and acidified with acetic acid and filtered. The residue consists of ethyl 2-amino - 4 - mercapto-5-*p*-chlorobenzeneazo-6-pyrimidylaminoacetate. It may be reduced with zinc and acetic acid by the process described in Example 1 and there is obtained 2-amino-6-mercapto-8-hydroxy - 9:10 - dihydropteridin which does not melt below 350° C.

EXAMPLE 10.

18.5 Parts of ethyl 2-amino-4-chloro-5-*p*-chlorobenzeneazo - 6 - pyrimidylaminoacetate, 15 parts of diethylamine and 450 parts of ethyl acetate are heated together under reflux for 5 hours. The ethyl acetate is then distilled off and the residue is triturated with water and filtered. There is obtained ethyl 2-amino - 4 - diethylamino - 5 - *p* - chlorobenzeneazo - 6 - pyrimidylaminoacetate which is crystallised from light petroleum and has m.p. 139° C. This substance may be reduced by means of zinc and acetic acid and is thus converted to 2-amino-6-diethylamino - 8 - hydroxy-9:10-dihydropteridin of m.p. 228° C. with decomposition.

EXAMPLE 11.

18.5 Parts of ethyl 2-amino-4-chloro-5-benzeneazo-6 - pyrimidylaminoacetate, 40 parts of methyl alcohol and 70 parts of 23% aqueous methylamine solution are mixed together and boiled under reflux for 1 hour. The mixture is then evaporated to dryness and the residue triturated with water and filtered. There is obtained 2 - amino - 4-methylamino-5-benzeneazo - 6 - pyrimidylaminoacetmethylamide of m.p. 241° C. If the process of this example be carried out in ethyl acetate solution instead of in methyl alcohol solution the product is ethyl 2-amino-4-methylamino-5-benzeneazo-6 - pyrimidylaminoacetate. Both of these substances may be reduced with zinc and acetic acid to give 2-amino-6-methylamino-8-hydroxy - 9:10-dihydropteridin which does not melt below 360° C.

EXAMPLE 12.

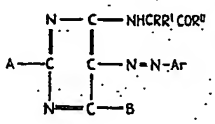
26 Parts of 4:6-dichloro-2-methylaminopyrimidine, 40 parts of glycine ethyl ester and 50 parts of ethanol are heated together under reflux for 20 hours. The mixture is then filtered and the residue is extracted with 15 parts of hot ethanol. The filtrate and extract are cooled and filtered. Water is then added to the filtrate and the solid so precipitated is filtered off and dried. It is ethyl 4-chloro-2 - methylamino - 6 - pyrimidylaminoacetate, m.p. 152° C. This ester is then caused to react with *p*-chlorobenzenediazonium chloride as described in Example 1 and ethyl 4-chloro-2-methylamino-5-*p*-chlorobenzeneazo-6-pyrimidyl - aminoacetate, m.p. 216° C. is obtained. 19 Parts of this substance, 65 parts of sodium ethylmercaptide and 1000 parts dioxan are boiled together for 1 hour, the mixture is then filtered and 900 parts of 50% aqueous ethanol are added to the filtrate. Ethyl 2-methylamino-4-ethylthiol-5-(*p*-chlorobenzeneazo)-6-pyrimidylaminoacetate, m.p. 120° C. is obtained.

EXAMPLE 13.

6 Parts of 2-amino-4-hydroxy-6-chloro-5 - *p* - chlorobenzeneazopyrimidine (m.p. 270° C., made by a process parallel to that described in Example 1), 10 parts of diethyl aminomalonate, 30 parts of dimethylformamide are mixed and allowed to stand for 48 hours and then filtered. The residue is crystallised from dimethylformamide and methanol. There is obtained diethyl 2-amino-4-hydroxy-5-*p*-chlorobenzeneazo - 6 - pyrimidylaminomalonate as red crystals, m.p. 252° C., which when reduced is converted into ethyl dihydroxanthopterin carboxylate.

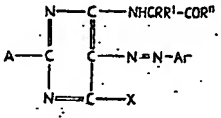
What we claim is:—

1. The new pyrimidine derivatives of the general formula:—



wherein A stands for hydroxyl, amino or alkylamino groups, wherein B stands for hydroxyl, thiol, alkylthio, amino or mono- or di-substituted amino groups, wherein Ar is an aryl radical which optionally may bear substituents, wherein R and R^1 may be hydrogen, hydrocarbon or substituted hydrocarbon radicals and one of them, but not both at once, may be the group $—COR^{11}$, and wherein R^{11} is hydrogen, a hydrocarbon radical, which may contain substituents, or a hydrocarbon-oxy radical, or an amino or mono-substituted amino group.

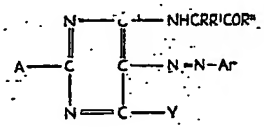
2. Process for the manufacture of the new pyrimidine derivatives claimed in claim 1 which comprises reacting a pyrimidine derivative of the formula:—



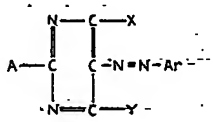
wherein A, Ar, R^1 and R^{11} have the meaning stated in claim 1 and wherein X stands for a halogen atom, with reagents capable of the replacement of an active halogen substituent by hydroxyl, thiol, alkylthio, amino or mono- or di-substituted amino groups.

3. Process as claimed in claim 2 wherein the reagents capable of the replacement of an active halogen substituent are chosen from alkali metal hydroxides; hydrogen sulphide and alkali metal hydrosulphides; alkali metal mercaptides; ammonia and primary and secondary amines.

4. Process for the manufacture of new pyrimidine derivatives of the formula



wherein A, Ar, R, R^1 and R^{11} have the meaning stated in claim 1 and wherein Y stands for a hydroxyl, thiol, amino or alkylamino group, which comprises reacting a pyrimidine derivative of the formula:—



wherein A, Ar and Y have the meaning stated above and wherein X stands for a halogen substituent, with an α-amino-aldehyde, -ketone or -carboxylic acid ester or amide of the formula:—

$$NH_2—CRR^1—COR^{11}$$

wherein R, R^1 and R^{11} have the meaning stated above.

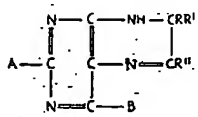
5. Process as claimed in claim 4 wherein, in the substance of formula:—

$$NH_2—CRR^1—COR^{11}$$

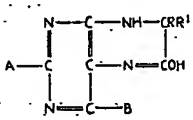
R^{11} is hydrogen or hydrocarbon, and wherein the said substance is brought into reaction in the form of a functional derivative thereof, the product being then subsequently liberated from its functional derivative by hydrolysis.

6. Process as claimed in claim 5 wherein the functional derivative is an acetal, oxime or semicarbazone.

7. Process for the manufacture of derivatives of dihydropteridin which comprises reacting upon the pyrimidine derivatives claimed in claim 1 by means of reducing agents so that the —N=N—Ar group is converted to an $—NH_2$ group, the so-formed amino-compound being then either permitted spontaneously, or constrained, for example, by heat, to undergo ring closure with formation of, where R^{11} is hydrogen or hydrocarbon, pteridin derivatives of the formula



or, where R^{11} is a hydrocarbon-oxy, amino or mono-substituted amino group, pteridin derivatives of the formula:—



8. Process for the manufacture of new pyrimidine derivatives as hereinbefore particularly described and ascertained

especially with reference to the foregoing Examples.

J. W. RIDSDALE,
Solicitor for the Applicants.

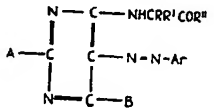
PROVISIONAL SPECIFICATION

New Pyrimidine Derivatives and their Use in the Manufacture of Pteridin Derivatives

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a Company incorporated under the laws of Great Britain, do hereby declare the nature of this invention to be as follows:—

This invention relates in the first place to new pyrimidine derivatives and to a process for making them.

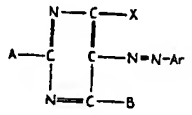
The new pyrimidine derivatives of this invention are compounds of the general formula:—



wherein A and B stand for hydroxyl, amino, alkylamino or thiol groups, the same or different, wherein Ar is an aryl radical which optionally may bear substituents, wherein R and R^1 may be hydrogen, hydrocarbon or substituted hydrocarbon radicals and one of them, but not both at once, may be the group $—COR^{11}$, and wherein R^{11} is hydrogen, a hydrocarbon radical or a hydrocarbon-oxy radical.

The said new pyrimidine derivatives are useful as intermediates in the manufacture of substances of chemotherapeutic value, for example of folic acid and related compounds.

They may be manufactured, and it is a further feature of the invention so to manufacture them, by a process which comprises reacting a pyrimidine derivative of the formula:



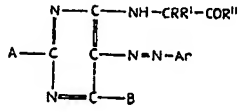
wherein A, B and Ar have the significance stated above and wherein X stands for a halogen atom, with an α-amino-aldehyde, -ketone or -carboxylic acid ester of the formula:—

$NH_2 CRR^1 COR^{11}$

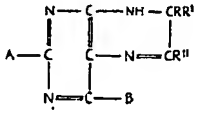
wherein R, R^1 and R^{11} have the significance stated above.

Where R^{11} is hydrogen or hydrocarbon, i.e. where the starting material is an amino-aldehyde or -ketone, this may be used in the form of a functional derivative thereof, for example of an acetal, oxime or semicarbazone thereof, the product being then subsequently liberated from e.g. its acetal, oxime or semicarbazone by hydrolysis.

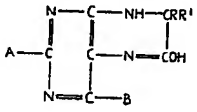
By yet a further feature of the invention we provide a process for the manufacture of derivatives of pteridin which comprises reacting upon the aforesaid pyrimidine derivatives of the formula



by means of reducing agents so that the —N=N—Ar group is converted to an $—NH_2$ group, the so-formed amino-compound being then either permitted spontaneously, or constrained, for example, by heat, to undergo ring closure with formation of, where R^{11} is hydrogen or hydrocarbon, pteridin derivatives of the formula:—



or, where R^{11} is hydrocarbon-oxy, pteridin derivatives of the formula:—



with elimination, as will be understood, in the first case of water and in the second case of the alcohol $R^{11} H$.

The said pteridin derivatives, which are dihydropteridins, may, when at least

one of R and R^1 is hydrogen, as is known, be converted to the corresponding pteridin by oxidation.

The invention is illustrated but not limited by the following Examples in which the parts are by weight.

EXAMPLE 1.

12 Parts of 2 - amino-4-methoxy-6-chloropyrimidine are dissolved in 50 parts of cold concentrated hydrochloric acid and the solution is heated on the steam-bath during 30 minutes. The mixture is then cooled, diluted with 200 parts of water and filtered. The solid residue consists of 2 - amino - 4 - hydroxy-6-chloropyrimidine, m.p. 261° C.

87 Parts of 2 - amino 4 - hydroxy-6 - chloropyrimidine, made as described above, are dissolved in 3600 parts of 0.2 N sodium hydroxide and 120 parts of sodium carbonate are added to the solution. A solution of benzenediazonium chloride prepared from 56 parts of aniline is added to stirred solution during one hour. The mixture is stirred for a further 12 hours and is then filtered and the solid residue is washed successively with water, alcohol and ether. It consists of 2-amino-4 - hydroxy - 5 - benzeneazo - 6 - chloropyrimidine.

38 Parts of aminoacetone hydrochloride are dissolved in 250 parts of ethyl alcohol and to the solution there is added a solution of 48 parts of semi-carbazide hydrochloride in 100 parts of water. The mixture is permitted to stand for 2 hours and is then filtered and the solid residue is recrystallised from aqueous alcohol and consists of aminoacetonesemicarbazone hydrochloride, m.p. 212° C.

107 Parts of aminoacetonesemicarbazone hydrochloride, made as described above, is added to a cold solution of 43.7 parts of sodium ethoxide in 600 parts of ethyl alcohol and the mixture is stirred for 2 hours. It is then added to a cold solution of 75 parts of 2-amino-4-hydroxy-5-benzeneazo-6-chloropyrimidine, made as described above, in 400 parts of dimethylformamide. It is allowed to stand for 12 hours and then filtered and the residual solid is washed successively with alcohol and water. There is obtained 2-amino-4-hydroxy-5- benzeneazo-6-acetonylaminopyrimidine semicarbazone, m.p. 206° C.

81 Parts of 2 - amino - 4 - hydroxy - 5-benzeneazo - 6 - acetonylaminopyrimidine-semicarbazone is dissolved in 250 parts of glacial acetic acid and to the solution there are added 1500 parts of 2N hydrochloric acid. The mixture is allowed to stand for 30 minutes and is then filtered and the residual solid is crystallised from ethyl alcohol. There is obtained 2-amino-4 - hydroxy - 5 - benzeneazo - 6 - acetonylaminopyrimidine hydrochloride of m.p. higher than 300° C. The free base liberated from this salt has m.p. 183° C.

51 Parts of 2 - amino - 4 - hydroxy - 5-benzeneazo - 6 - acetonylaminopyrimidine hydrochloride are dissolved in 250 parts of glacial acetic acid and the solution is stirred and heated to 80—90° C. and 40 parts of zinc dust are added to it during 30 minutes. The mixture is then filtered and 500 parts of 5N hydrochloric acid are added to the filtrate which is then again filtered and the solid residue consists of 2-amino - 6 - hydroxy - 8 - methyl - 9 : 10-dihydropteridin hydrochloride monohydrate, m.p. not below 300° C.

16.3 Parts of 2 - amino-6-hydroxy-8-methyl - 9 : 10 - dihydropteridin hydrochloride monohydrate are dissolved in 1200 parts of 0.25 N aqueous sodium hydroxide solution. To the stirred solution there are added 243 parts of 0.2 M aqueous potassium permanganate solution during one hour. The mixture is then filtered and carbon dioxide gas is passed into the filtrate which is then again filtered. The solid residue consists of 2-amino-6-hydroxy-8-methylpteridine, m.p. not below 300° C.

EXAMPLE 2.

1.2 Parts of glycine ethyl ester hydrochloride are added to a solution of 0.53 part of sodium ethoxide in 5 parts of ethyl alcohol the mixture being stirred for 30 minutes. It is then added to a solution of 1 part of 2-amino-4-hydroxy-5-benzeneazo-6-chloropyrimidine, made as described in Example 1, in 5 parts of dimethylformamide and the mixture is allowed to stand for 12 hours and is then filtered. The solid residue is washed successively with ethyl alcohol and water and consists of 2-amino-4-hydroxy-5-benzeneazo - 6 - carboethoxymethylaminopyrimidine which, when crystallised from *n*-butanol has m.p. 238° C.

1 Part of 2-amino-4-hydroxy-5-benzeneazo - 6 - carboethoxymethylaminopyrimidine, made as described above, is dissolved in 5 parts of glacial acetic acid and the solution is stirred and heated to 80—90° C. and then an excess of zinc dust is added slowly. The fine suspension of white solid is decanted from unused zinc dust and is then centrifuged. The so separated solid is dissolved in boiling 0.25 N sulphuric acid and from the solution, when cold, there are filtered off colourless crystals of 9 : 10-dihydroxanthopterin sulphate, m.p. not below 300° C.

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Solicitor for the Applicants.

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